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Visual evoked potentials

The effects of glaucoma on the latency of the multifocal visual evoked potential

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Delays in signal conduction are not great enough to be useful clinically

In this issue of the *BJO* (p 1132) the paper by Rodarte *et al* reports on the effect of glaucoma on the multifocal multichannel visual evoked potential (mfVEP), specifically its effect on signal latency.¹ Many previous publications have established that there is a loss of mfVEP amplitude in glaucoma.^{2–5} This paper confirms that there are also some measurable effects on latency, but the delays in signal conduction are not great enough to be useful clinically with only 40% showing significant change. As a relative negative finding this is important if the mfVEP is to be used in the diagnostic setting.

It is consistent with our understanding of the mechanisms of cell death in glaucoma, where demyelination is not a feature, in contrast to optic neuritis where marked latency delays are the hallmark. In fact in our recent study,⁶ large mfVEP latency delays in the recovery phase of a first episode of optic neuritis may even be predictive of the later onset of multiple sclerosis. A recent paper by Danesh-Meyer *et al* has also reported mfVEP amplitude reductions in compressive optic neuropathy,⁷ with some latency delays but not as marked as in optic neuritis (personal communication). The relative losses of amplitude versus delay may help separate not only disease types, but possibly prognosis in these conditions. It had been hoped that latency delays in glaucoma may be useful as an early marker in glaucoma, since there are many previous studies on the conventional VEP (cVEP) where some delays were identified. Also, latency has greater reproducibility and less inter-subject variability so would therefore be a useful parameter to measure. Unfortunately, this study confirms that the delays are not

substantial enough to use in diagnosis. We had previously found similar results with the Veris (Electro-Diagnostic Imaging, San Mateo, CA, USA) multifocal system using quadrantic latency averages,⁸ and also with the AccuMap system (Objectivision, Sydney, Australia) with individual latencies.⁹

Many papers have examined the cVEP in glaucoma and identified latency changes.^{10–11} In an early study with an age corrected cohort of patients with open angle glaucoma (OAG) and ocular hypertension (OHT), the full field pattern VEP showed about 50% and 25% of patients, respectively, to have a delay in latency compared to normals.¹² The predominant effect in other studies was a delay in p100 latency of around 20 ms^{12–13} and a phase shift in the steady state pattern visually evoked potential (PVEP).^{14–15} Horn *et al* reported that the peak time of a blue-yellow VEP had high sensitivity, and could be used to monitor progression.¹⁶ The consensus appears to be that for the cVEP there is definitely some delay detected, but the ability of the tests to reliably separate glaucoma from normals varies greatly between studies.

The amplitude of the mfVEP shows substantial reductions in glaucoma but latency delays are only mild

Rodarte *et al* in the current study raise the point that their results seem to be in contrast to a recent paper on cVEPs¹⁷ where extremely high sensitivity and specificity (100%) for the latency of the VEP in glaucoma was reported. It is interesting to note in that paper that even the OHT subjects (IOP >21 mm Hg but normal discs) were also all delayed and clearly demarcated from the

controls. This implies very early pressure related dysfunction in a group that may not all be destined for clinical glaucoma, yet the mfVEP only identified minor delays in established glaucoma.

There is no clear explanation for the difference in the findings of these two reports, but clearly it is important to conduct a study to compare the two types of VEP (conventional and multifocal) in the same individuals with early glaucoma. This should help confirm known differences between the two tests and establish if there is a difference in the effects of glaucoma on latency.

Fortune and Hood¹⁸ have already done a comparative study in normals and shown that transient pattern reversal cVEP responses to relatively large field stimuli cannot be related simply to the sum of local mfVEP responses recorded with fast m-sequence stimulation. The amplitude of the full field response grew dramatically as the sequence was slowed, which was the result of several factors, including loss of hemifield polarity inversion, increased dominance of the lower hemifield, and overall growth in amplitude with slower reversal rates.

The cVEP is dominated by the central macular responses, and the lower central field more than upper, depending on electrode position. It is recorded with a uniform stimulus check size and a slow reversal rate throughout the field. It is a summed response from multiple striate cells of different orientation, and there can be different cancellation effects depending on the individual's underlying cortical convolutions. This may be why many previous full field studies have failed to show consistent amplitude loss in glaucoma, as location of the field loss (peripheral versus central, or superior versus inferior) may produce different effects on the net recorded response.² It could also theoretically change the latency, as the shape and timing of the waveforms differ in different parts of the field, unlike the electroretinogram (ERG) which has the same shaped waveform throughout.

There are several differences between the two test techniques, which could contribute to differing results. The mfVEP dartboard stimulus is cortically scaled, with larger checks in the periphery and smaller checks in the centre, to

adjust for signal density and ensure similar order of magnitude response throughout the tested field. cVEPs, on the other hand, use the same spatial frequency for the whole field. VEP latency is reported to be shortest for the optimal spatial frequency, so the cVEP may be a composite of some optimally stimulated receptive fields, and some not so. We presume the spatial frequencies are close to optimal in the mfVEP,¹⁸ but this may not be the case for optimal disease detection.

Secondly, VEP latency decreases with increasing contrast. The mfVEP uses high contrast, although it can be recorded to low contrast stimuli as well (which may be a reasonable strategy in glaucoma). There could be different contrast-response functions such that non-saturated VEP latencies may show further delay in glaucoma that are not apparent when the VEP stimulus is optimal and the latency is at its shortest. Thirdly, the stimulation rate differs substantially between the two tests. In the cVEP the rate is slow reversal—for example, a few cycles per second. In the mfVEP the pseudorandom sequence determines a mixture of reversal rates at many different frequencies, but overall the stimulation rate is much faster than cVEP. One could postulate that there may be a greater contribution from faster conducting cells (magnocellular) in the mfVEP, but this is not confirmed. In the above study by Fortune and Hood¹⁸ the mfVEP latencies were indeed faster, but this occurred with slowed stimulation rates as well, possibly as a result of factors mentioned above. In our check size study the peripheral responses were about 5 ms faster than responses from the central rings.¹⁹

A further difference is that while it is thought that both tests have their generators primarily in the V1 cortex,²⁰ the late components of the cVEP may be derived from extrastriate areas.^{21–22} Whether this could account for variable effects on latency in glaucoma is also speculative.

Therefore, while it is clear there are some effects on the latency of the mfVEP in glaucoma, these changes do not appear to be useful clinically. They are also not of the same magnitude as found by Parisi *et al* in cVEPs.¹⁷ The two test stimuli and recording techniques are quite different, which may account for at least some of the reported

discrepancy. Further studies are certainly warranted.

Conventional forms of perimetry are dependent on subject responses and require a high level of cognitive ability to perform the test. This makes these tests challenging for individuals, particularly the elderly and children, and has driven the push towards forms of objective perimetry. The mfVEP shows promise as a means of achieving such a clinically useful test, using local amplitude reductions. It is necessary to use multiple channels, with a minimum of a vertically and horizontally oriented pair of bipolar electrodes so that all underlying dipole orientations are detected. In glaucoma with established field loss it has been found to be 95% sensitive and 90% specific, and can provide complementary functional data to current subjective methods. When investigating glaucoma subjects who have poor perimetric technique it can be extremely helpful. In investigating other optic nerve pathology, substantial delays are seen in optic neuritis, while in unexplained visual loss combining the mfVEP with the mFERG can help localise the level of the disease to retina or optic nerve/cortex.

The main limitation of the mfVEP as a form of objective perimetry remains intra-individual reproducibility and noisy recordings which can lead to false positives. There is still a level of patient cooperation required, together with technician experience to recognise noise such as alpha rhythm (patient losing concentration), muscle noise, and other artefacts. Further developments in mVEP technology should be directed towards improving signal to noise ratios and thereby both increasing sensitivity and reducing variability.

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